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The future of cancer therapy

PROMs in clinical research: the EORTC experience

15th June 2022,

OECI Oncology Days 2022 -Scientific Sessions

Valencia, Spain

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Statistics/QOL Department
European Organization for Research and Treatment of Cancer
Brussels, Belgium

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DISCLOSURE INFORMATION

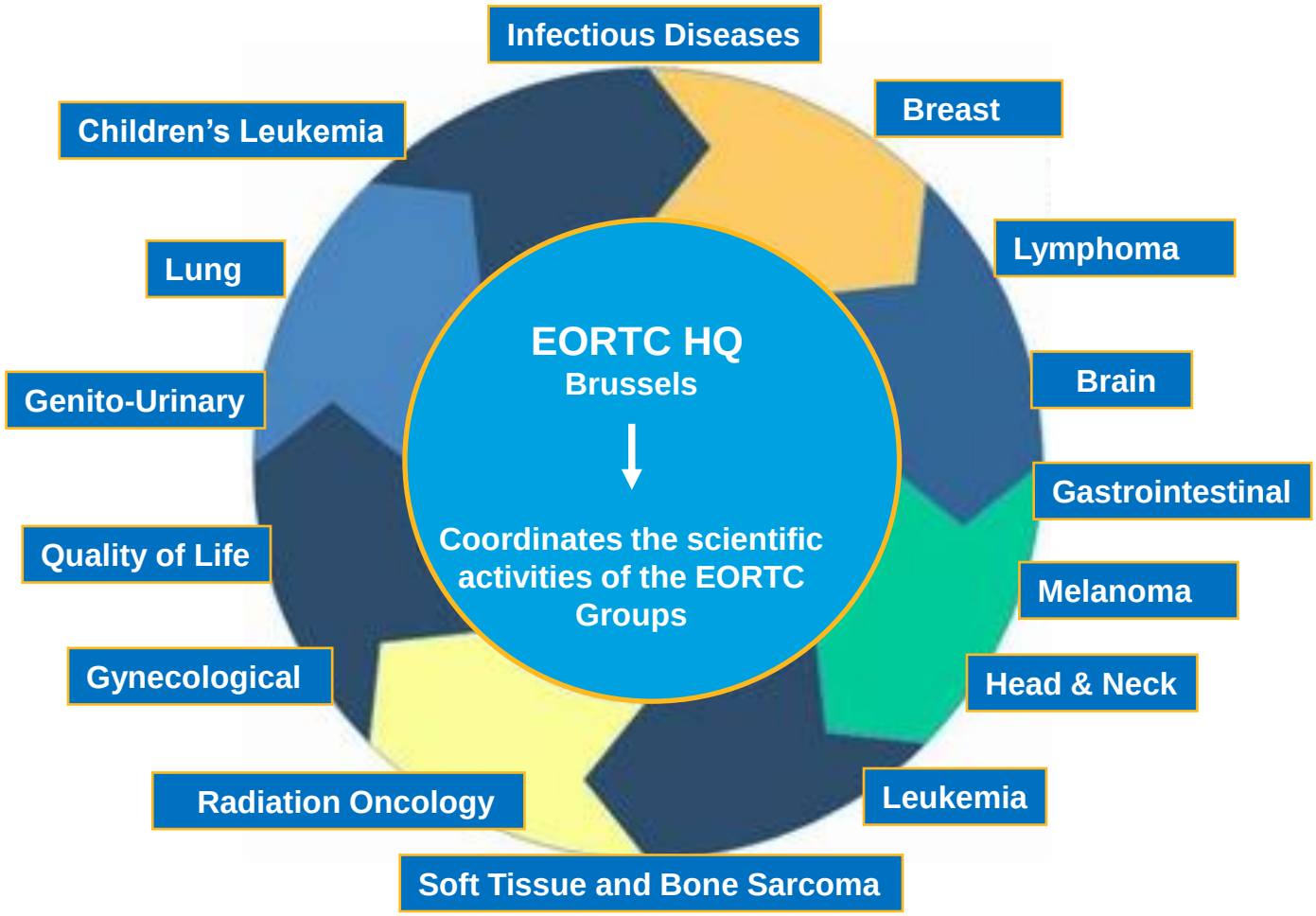
I have no conflicts of interest

I am a full-time employee of the EORTC

European Organization for Research and Treatment of Cancer (EORTC)

- Private and not-for-profit organization created in 1962
- Main mission: promote and conduct research to improve cancer survival and improve quality of life
- Core activity: conduct clinical trials
  - International
  - Multidisciplinary
  - Develop new treatments
  - Define new standards of care
  - Large academic trials

EORTC Structure: 21 clinical groups of 600 centers across the EU



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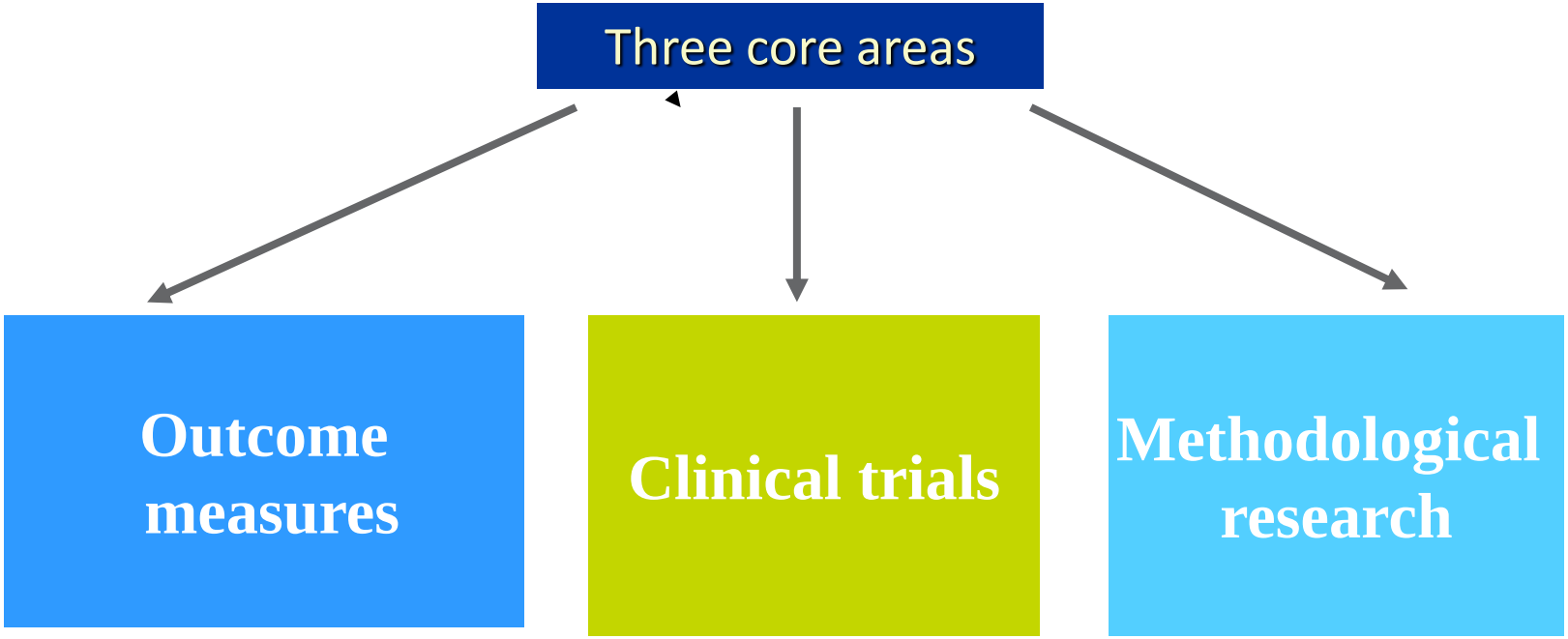
The Volunteers: network of the EORTC Quality of Life Group: 2019 (Croatia)

Quality of Life environment at the EORTC

Small department to oversee QOL research across the EORTC



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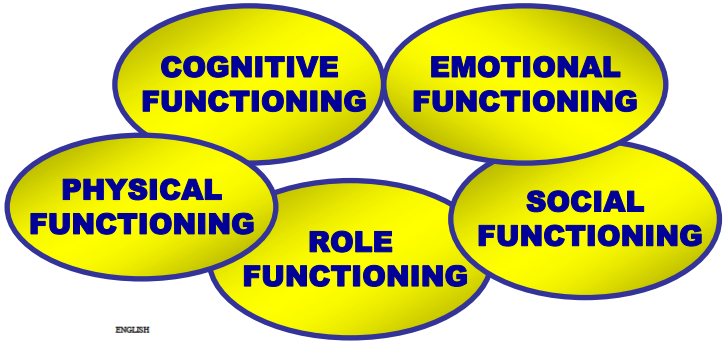
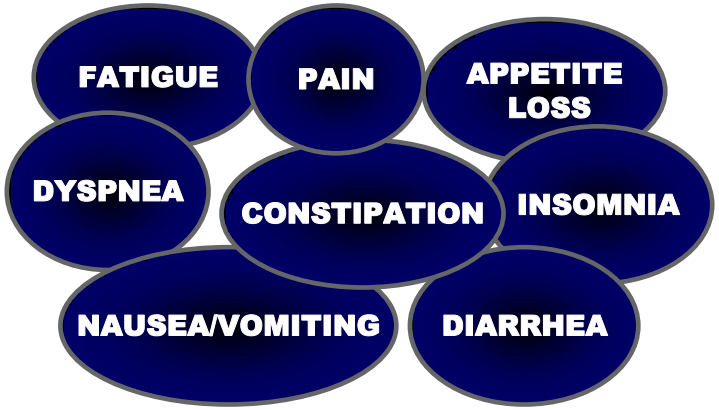
QOL and outcome measures

QOL Parameters for EORTC QLQ-C30 tool





ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

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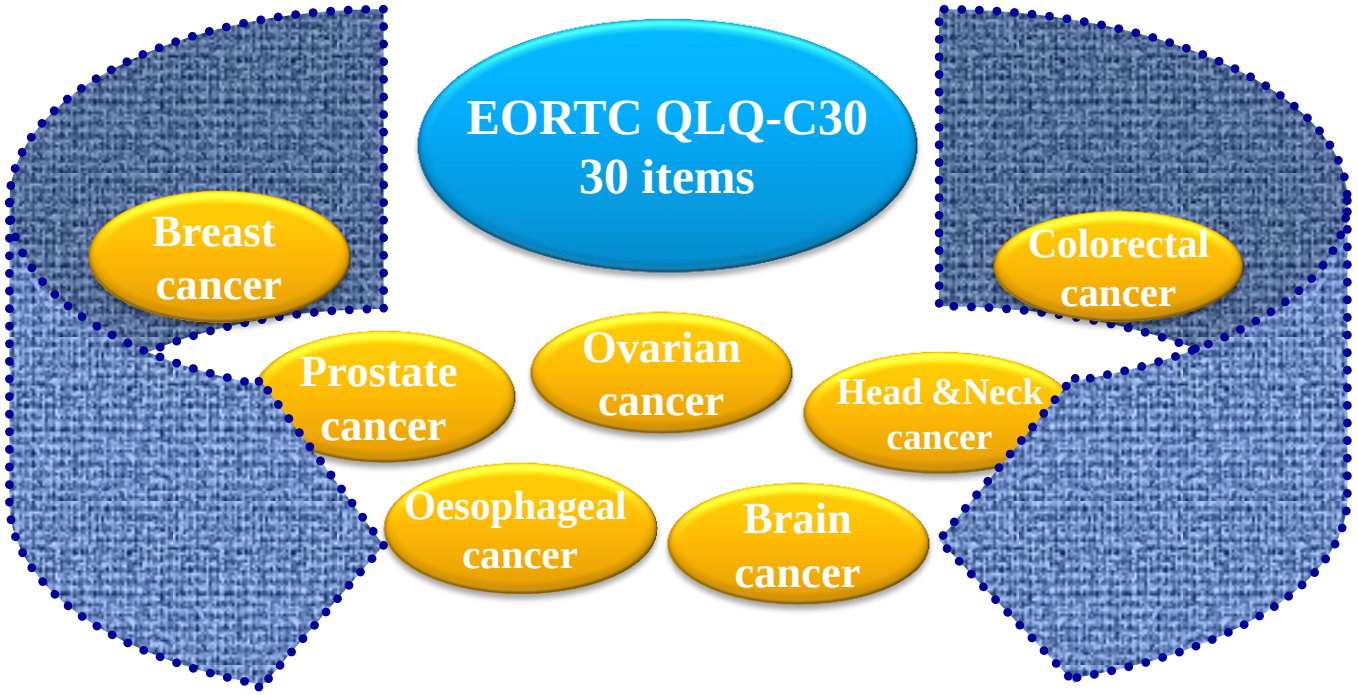
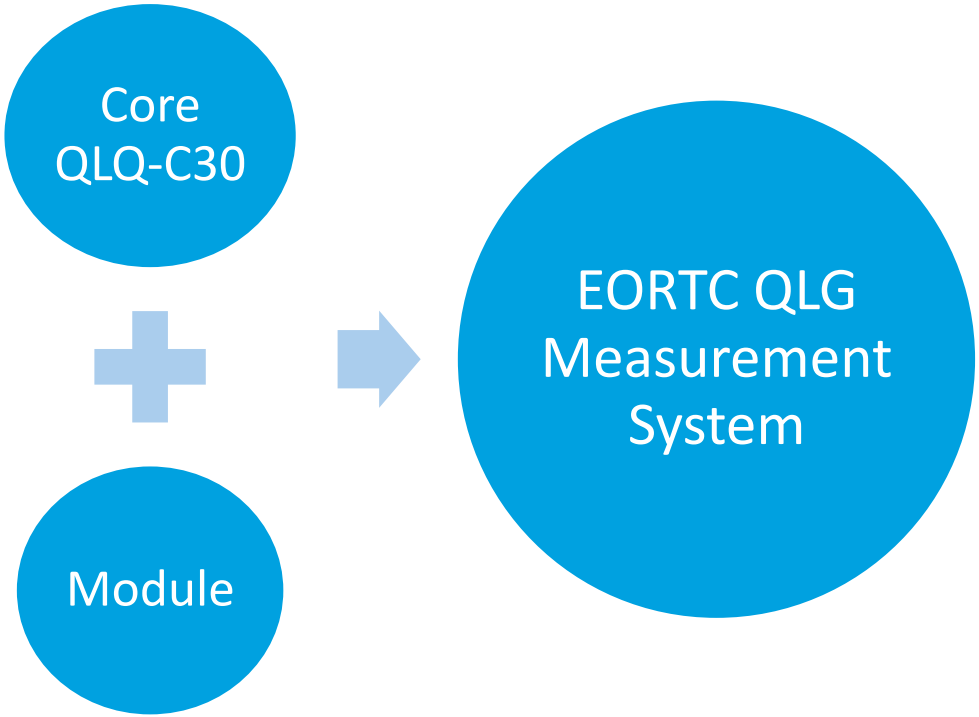
The EORTC Modular Approach: Disease specific



The EORTC Modular Approach: Disease specific

- **Modules**, designed to be administered in conjunction with the QLQ-C30, and specific to:
  - **Tumour types**
  - **Treatment modality**
  - **HRQoL domain**
  - **Population**



72 modules (32 fully validated)

Translations
What languages are EORTC measures in?

الحب Love	الحكمة Wisdom
السّلام Peace	الحياة Life

From Arabic to Zulu

QLQ-C30 – More than 100 translations!

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A more flexible approach to PRO assessment …

EORTC Item Library

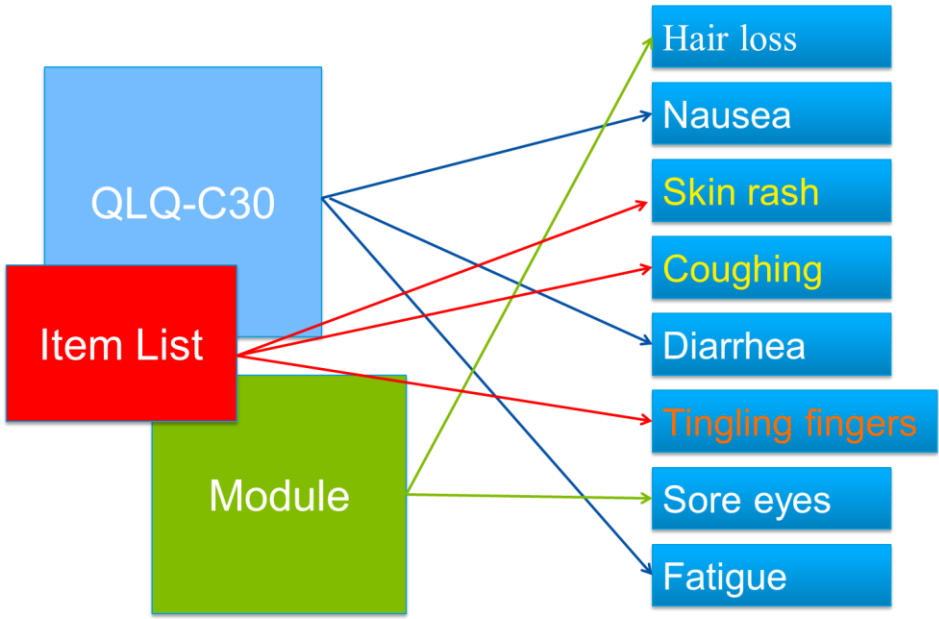
FDA correctly points out the inability of 'static questionnaires' to ensure content validity in trials of new drugs

Select Items specific to the research hypothesis.

- reduce burden by minimizing number of questions
  - ✓ Less redundant or irrelevant questions
- Increased flexibility and efficiency
  - ✓ More tailored to the needs of specific treatments and populations

Item library: Allows to create ad-hoc item lists specific to a given trial

https://www.eortc.be/itemlibrary/



EORTC CAT Core

Computerized adaptive test (CAT)

- Works in conjunction with item banks/libraries.
- Optimises measurement **precision & flexibility** based on Item Response Theory
  - ✓ CAT version of the EORTC QLQ-C30 has been developed
  - ✓ Item selection is tailored to the individual based on responses to prior items
  - ✓ CAT item banks (260 items) fully validated for the EORTC QLQ-C30 domains
- Evaluations indicate higher measurement precision and thereby increased statistical power of the CAT compared to the standard QLQ-C30.
- CAT software under validation for **use in clinical trials** (expected release 01/09/22)

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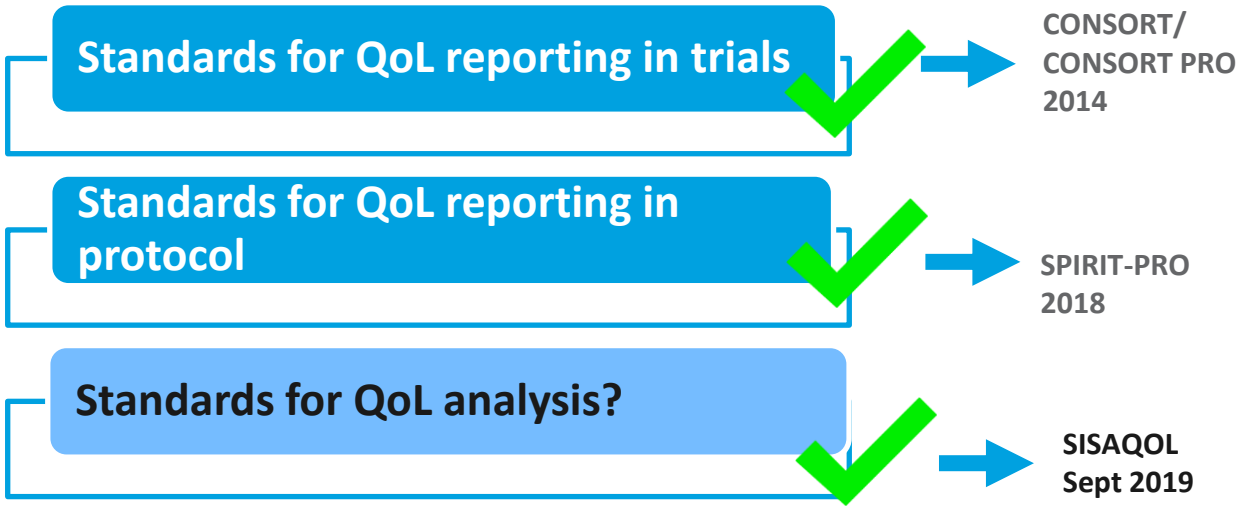
Methodological standards in trials

Is there a lack of gold standards for QoL parts of trials?



No standardization in the use and analysis of QoL data → Two identical trials being analyzed in different ways, leading to different conclusions →

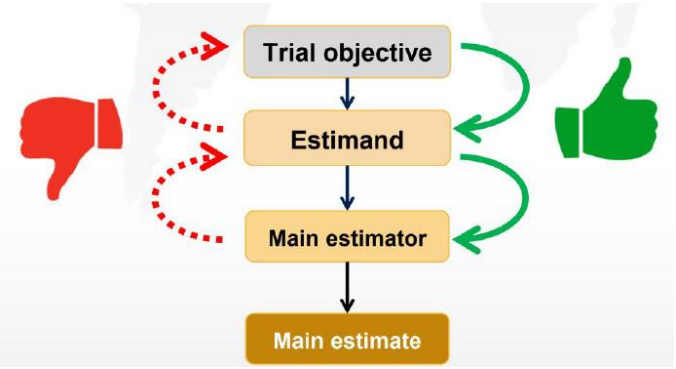
- Different interpretation of findings depending on how data is analyzed
- Undermine the credibility of the QoL field

A Consortium "Setting International Standards in Analysing Quality of Life" (SISAQOL)

SISAQOL-IMI

SISAQOL-IMI recommendations framework

	Confirmatory Objective: Clinical benefit / Treatment Efficacy		Descriptive Objective: *Tolerability (?)*
	Superiority	Equivalence / Non-inferiority	
Magnitude of change	Recommendation	Recommendation	Recommendation
Response patterns / profile	Recommendation	Recommendation	Recommendation
Time to improvement	Recommendation	Recommendation	Recommendation
Time to worsening	Recommendation	Recommendation	Recommendation
Responder improvement	Recommendation	Recommendation	Recommendation
Responder worsening	Recommendation	Recommendation	Recommendation



- Help align the objective with the design and statistical analysis
- And ensure that the PRO results and conclusions address the intended PRO objective.

https://www.sisaqol-imi.org/

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Clinical Trials and QOL

EORTC Clinical trials with HRQOL outcomes
Total HRQOL on clinical (since 1990)

Type of Trial	Total
Phase II	20
Phase II/III	40
Phase III	190

Selected top line results of key EORTC trials with QOL

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

ABSTRACT

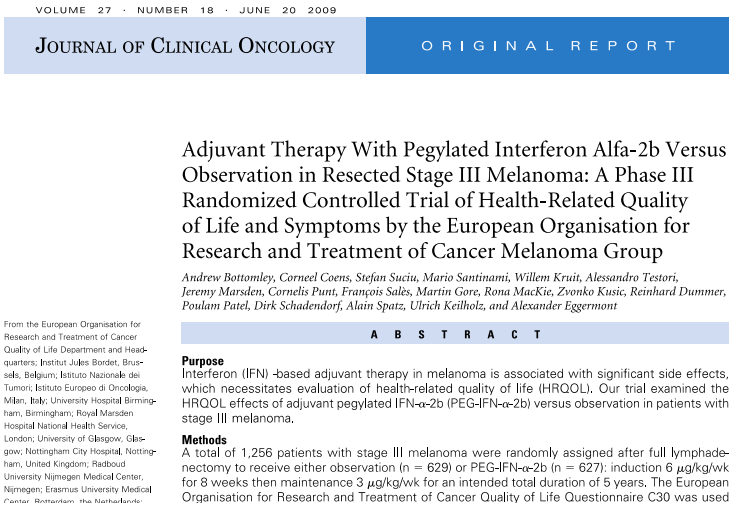
BACKGROUND

Glioblastoma, the most common primary brain tumor in adults, is usually rapidly fatal. The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by adjuvant radiotherapy. In this trial we compared radiotherapy alone with radiotherapy plus temozolomide, given concomitantly with and after radiotherapy, in terms of efficacy and safety.

From the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (R.S., R-C.J., R.O.M.); Princess Margaret Hospital, Toronto (W.P.M.); Daniel den Hoed Oncology Center–Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands (M.J.B.); the University of Tübin-

- Demonstrated that chemotherapy with the drug temozolomide in conjunction with radiotherapy increases survival for patients with glioblastoma (the most common type of malignant brain tumor) with no negative impact on QOL
- The drug was approved by FDA/ EMA with supporting QOL

NEJM 2005



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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adjuvant Therapy With Pegylated Interferon Alfa-2b Versus Observation in Resected Stage III Melanoma: A Phase III Randomized Controlled Trial of Health-Related Quality of Life and Symptoms by the European Organisation for Research and Treatment of Cancer Melanoma Group

Andrew Bottomley, Corneel Coens, Stefan Suciu, Mario Santinami, Willem Kruit, Alessandro Testori, Jeremy Marsden, Cornelis Punt, François Salès, Martin Gore, Rona MacKie, Zvonko Kusic, Reinhard Dummer, Poulam Patel, Dirk Schadendorf, Alain Spatz, Ulrich Keilholz, and Alexander Eggermont

From the European Organisation for Research and Treatment of Cancer Quality of Life Department and Headquarters; Institut Jules Bordet, Brussels, Belgium; Istituto Nazionale dei Tumori; Istituto Europeo di Oncologia, Milan, Italy; University Hospital Birmingham, Birmingham; Royal Marsden Hospital National Health Service, London; University of Glasgow, Glasgow; Nottingham City Hospital, Nottingham, United Kingdom; Radboud University Nijmegen Medical Center, Nijmegen; Erasmus University Medical

A B S T R A C T

Purpose

Interferon (IFN) -based adjuvant therapy in melanoma is associated with significant side effects, which necessitates evaluation of health-related quality of life (HRQOL). Our trial examined the HRQOL effects of adjuvant pegylated IFN-α-2b (PEG-IFN-α-2b) versus observation in patients with stage III melanoma.

Methods

A total of 1,256 patients with stage III melanoma were randomly assigned after full lymphadenectomy to receive either observation (n = 629) or PEG-IFN-α-2b (n = 627): induction 6 μg/kg/wk for 8 weeks then maintenance 3 μg/kg/wk for an intended total duration of 5 years. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 was used

- EORTC phase 3 RCT showed the clinical benefits of Adjuvant Therapy With Pegylated Interferon Alfa-2b Versus Observation in Stage III Melanoma.
- PEG-Interferon was approved by FDA based on clinical results. The QOL data showed some major negative impact on patients QOL compared to placebo, so the treating physician can inform patients of the negative impact on QOL to patients

JCO 2009

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More on Research at the EORTC

Analysis and meta analysis studies

- Prognostic value of QoL
- Reference values for QoL
- Interpretational guidelines: MID/thresholds
- Data sharing: https://www.Eortc.Org › data-sharing

Long-term follow-up / Survivorship

- Late Toxicity
- Long-term Quality of Life
- QoL tools for survivors

Summary

VS

Current times – 2022

- QoL or PROs is not a new concept
- Scepticism is much lower
- Robust standardised measures
- Hundreds of translations
- Dozens of disease measures
- Fewer Investigators are debating the added value of QoL

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Summary

- Many more studies worldwide have shown the added value of QoL: but almost always as a secondary endpoint
- FDA and EMA value QoL.
- However, standards must continue to improve
  - ❑ Classic trial design → Novel trial design
- We will expect to see more use of QoL in the coming decade and better electronic tools
- QoL constitutes an important aspect of cancer research and care: it gives voice to patients, putting their experience at the forefront.

Thank you

Special thanks to:

- Andrew Bottomley
- Corneel Coens
- Madeline Pe
- Hugo Vachon
- Dagmara Kulis
- Irina Ghislain
- EORTC QoL Group

- EORTC Item library: https://www.eortc.be/itemlibrary/
- EORTC CAT: https://qol.eortc.org/cat/
- SISAQOL-IMI: https://www.sisaqol-imi.org/
- EORTC QLG: https://qol.eortc.org/

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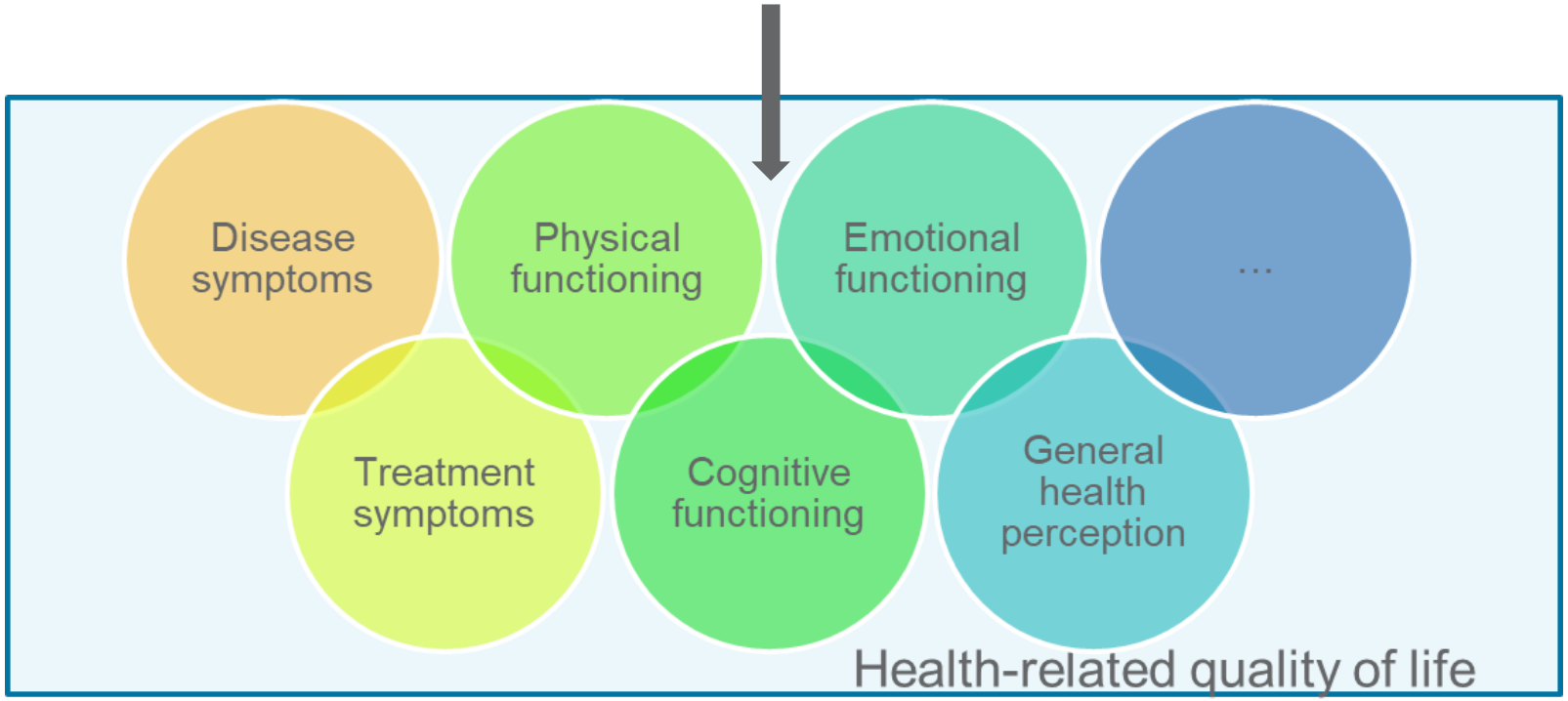
Supplementary slides

Working definition of HRQOL

Subjective Multi-dimensional Dynamic



EORTC network in 2016 – key facts and figures

- 200,000 patients in follow-up in the databases from 35 countries
- 4000 patients entered into clinical trials every year
- **150 trials currently open to patient entry**
- **25 new trials opened in 2015, 15 with QOL endpoint**
- **200 trials with QOL in since 1996**
- 600 institutions from 35 countries involved in our trials
- **100 members of the QOL group since 1986**
- 450 publications every 2 years (JCO, NEJM, LTO, etc)

EORTC CAT Core

- Item banks developed for computerized adaptive testing (CAT) of 14 dimensions of the QLQ-C30 (global health status/QoL not included)
  - Administered electronically
  - Possibility to create short forms for paper administration
- For each QLQ-C30 dimension (item bank), the CAT:
  - Measures the same dimensions as the original QLQ-C30
  - Includes the original C30 items
  - Uses EORTC “item style” (e.g., same response options, timeframe, etc.)

https://qol.eortc.org/cat/

Shift in trial design

Old model
- Classic trial design
  - Fixed population
  - Fixed intervention
  - Fixed characteristics
- PRO instruments
  - General coverage
  - Paper administration
  - Static questions

New model
- Novel trial design
  - Basket trials
  - Umbrella trials
  - Adaptive designs
- PRO instruments
  - Tailored topics
  - ePRO
  - Dynamic question set

Increased uncertainty in validation, implementation and interpretation